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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/873,601	06/12/1997	GARRY P. NOLAN	A-63915/DJB/	2070

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EXAMINER
FRIEND, TOMAS H F

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 06/17/2002 3/

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File copy	08/873,601	NOLAN ET AL.	
	Examiner	Art Unit	
	Tomas Friend	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Examiner's Name

The name of the examiner of this application has changed from Thomas Prasthofer to Tomas Friend.

Status of the Application

Receipt is acknowledged of a response to an office action with amendment on 25 February 2002 (Paper No. 30).

Status of the Claims

Claims 1-8, 27, 28, 31, 32, 34, and 39 were cancelled by applicants in Paper No. 23. Claims 9-26 were cancelled by applicants in paper No. 18. Claims 44-47 were cancelled by applicants in Paper No. 27. Claims 29, 30, 33-38, and 40-42 were withdrawn from further consideration by the examiner in Paper No. 16, the election having been made without traverse in paper No. 15. Claims 58- 79 were pending in the application. Applicants added new claims 80 in Paper No. 30. Claims 58-80 are pending in the present application and are being examined on their merits.

Withdrawn Rejections

1. The rejections of claims 58-79 under 35 U.S.C. 112, first paragraph (New Matter), are withdrawn in response to applicants' arguments.

Maintained Rejections

The statutory basis for each of the following rejections may be found in a prior office action.

2. Claims 58-79 (and new claim 80) are rejected under 35 U.S.C. 101 for reasons made of record in Paper No. 28.

Applicants argue that the present specification "*discloses a wide variety of specific utilities for the claimed methods.*" Applicants cite passages on pages 42 and 52 of the specification in which utilities related to chemotherapeutic agents, anti-tumor activity, and modifying drug toxicity.

Applicants' argument has been carefully considered and found not to be persuasive. Applicants' diverse list of possible utilities (including cosmaceuticals, bone disease, diabetes, cancer, and cardiovascular disease, for example) is essentially the equivalent of "*biological activity,*" which is not a specific and substantial utility. The claimed methods are methods of screening that detect altered phenotypes in cells that express libraries of enzyme complexes and molecular scaffolds. The claimed methods provide no screening steps that result in a product with specific and substantial utility. Consequently, one of skill in the art, in light of the disclosure, would understand that the claimed methods would provide results which, after additional research and development, may lead to the production or identification of products that would provide a benefit to the public. What the specific benefit would be, however, would not be understood from and is not identified in the specification.

Applicants argue that the claimed methods are supported by a well-established utility and cite Minshull et al. U.S. Patent No. 5,837,458 and Khosla et al. U.S. Patent No. 5,672,491 in support of their argument.

Applicants' argument has been carefully considered and found not to be persuasive. The cited references involve polyketides and their synthesis. Polyketides have a well-established utility. The presently claimed methods are disclosed as resulting in the identification or production of polyketides or any other products with a well-established utility.

The rejection is maintained.

Maintained Rejections – 35 U.S.C. 112, first paragraph

3. Claims 58-79 (and new claim 80) are also rejected under 35 U.S.C. 112, first paragraph (enablement) for reasons made of record in Paper No. 28.

Applicants argue that the examiner "*has misconceived the relationship between a rejection for lack of utility under §101 and §112, first paragraph*" because the examiner "*appears to suggest that the utility rejection under §101 derives from lack of sufficiently enabling disclosure under§112, first paragraph.*" Applicants' argument has been carefully considered and found not to be persuasive. The examiner has provided reasoning for the rejection of claims 58-80 under 35 U.S.C. 101. Applicants' are referred to M.P.E.P. 706.03(a) page 700-47 for an explanation of the relationship between utility rejections and rejections under 35 U.S.C. 112, first paragraph.

Applicants argue that the specification provides specific examples of how to identify cells with altered phenotypes, provides lists of classes of enzymes, and provides guidance with respect to expressing exogenous scaffolds and enzymes.

Applicants' argument has been carefully considered and found not to be persuasive. The claimed methods detect altered phenotypes in cells that express libraries of enzyme complexes made by joining recombinant enzymes with molecular scaffolds. The claimed methods encompass all changes in phenotype, all enzymes, all scaffolds (i.e. any nucleic acid or protein that can bind to (with or without specificity to two or more enzymes), and all cells. The specification provides no guidance that would allow one of ordinary skill in the art to correlate libraries, scaffolds, phenotypic changes, and assay methods. The specification provides no working examples of the claimed method. Attempting to screen for phenotypic changes in any cell caused by any combination of any exogenous scaffold library with any library of expression vectors that encodes two or more enzymes per vector was highly unpredictable in the art. Even taking into account the knowledge of one of ordinary skill in the art with respect to the compatibility of a particular vector with a particular cell type and what method steps to use for screening a particular change in phenotype, one of ordinary skill would be required to experiment in order to determine what library would work with a particular scaffold library to produce a phenotypic change in cells that is not caused by either library alone, for example.

Accordingly, the lack of specification teaching regarding what combinations of enzyme complexes, scaffolds, cells, and phenotype changes are likely to produce positive results, the burden of undue experimentation falls on one wishing to use the claimed invention.

4. Claims 58-79 (and new claim 80) are rejected under 35 U.S.C. 112, first paragraph, (Written Description) for reasons made of record in Paper No. 28.

Applicants argue that "*the examiner argues that adequate written description requires representative working embodiments of cells, enzymes, scaffolds, and altered phenotypes.*" Applicants' argument has been carefully considered and found not to be persuasive. The relevant portion of the rejection made in Paper No.28 is reproduced with emphasis below.

"With respect to adequate disclosure **of the scope** of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the claimed method is enabled and that *applicant had possession **of the full scope** of the claimed invention*, i.e. a method of screening a plurality of cells for a change in phenotype. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). **The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.**

Applicants argue that the specification provides details to satisfy the written description requirement. Applicants support this argument by citing parts of the disclosure that describe scaffolds, enzymes, libraries of scaffolds and enzymes, and detection of phenotypes.

Applicants' argument has been carefully considered and found not to be persuasive. The claimed method, in order to be practiced commensurate in scope with the claims, requires that one be in possession of both the method steps and materials required to perform the method. The claimed scope of the method steps involving detection of a phenotypic change, for example,

encompasses any means of detecting any change of phenotype for any cell. Applicants do not appear to have been in possession of method steps commensurate in scope with the claims at the time of filing. The materials required for one to practice the claimed invention commensurate in scope with the claims encompass libraries of all scaffolds, libraries all enzymes, and all cells, for example. Applicants do not appear to have been in possession of all required materials at the time of filing. It is noted that applicants are not required to be literally in possession of all methods and materials. Applicants can show possession by providing representative examples of using the claimed method. Applicants have not provided representative examples of the claimed method. Instead, applicants have provided lists of materials that can be used and lists of phenotypic changes that can be detected.

Maintained Rejections – 35 U.S.C. 112, second paragraph

5. Claims 58-79 (and new claim 80) are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, for reasons made of record in Paper No. 28.

Applicants argue that one of ordinary skill construing the claims in view of the disclosure would understand that screening and detecting are synonymous and that detecting an altered phenotype is included in screening. Applicants also argue that contacting cells with reagents is also encompassed and that the means of detecting the altered phenotype depend on the phenotypic change being detected.

Applicants' arguments have been carefully considered and found not to be persuasive. The rejected claims are drawn to a method of screening in which the final step recites "*screening said plurality of cells*" without providing any method steps to particularly point out what the screening method is.

6A. Claim 58 remains rejected over the term "exogenous scaffolds" for reasons made of record in Paper No. 28.

Applicants argue that "*the examiner contends claim 58 fails to recite any nucleic acid or amino acid sequences of specific enzymes.*" Applicants' argument has been carefully considered and found not to be persuasive. The rejection of the claim is not that the claim "*fails to recite*

any nucleic acid or amino acid sequences of specific enzymes." The rejection made in Paper No. 28 is reproduced below with emphasis.

"*It is not clear what the metes and bounds of the claimed invention are with respect to structures of nucleic acids and peptides (or proteins) that are 'exogenous scaffolds.' There are no limitations with respect to nucleic acid or amino acid* ***sequences, the lengths*** *of the scaffolds* ***or how one is to determine whether or not the scaffolds possess binding sites specific for the enzymes in the claim***."

For example, any vector DNA could potentially be an "*exogenous scaffold*." Any method that involves expressing a library of enzymes as claimed could be considered to automatically include a scaffold because the DNA could potentially bind some enzymes in the library.

6B. Claim 59 remains rejected over the term "*exogenous bioactive agent precursor*" for reasons made of record in Paper No. 28.

Applicants argue that a person skilled in the art would understand that screening would be performed both in the presence and absence of the "*exogenous bioactive agent precursor*" (i.e. a negative control). Applicants' argument has been carefully considered and found not to be persuasive. While the claims are to be read in light of the specification, limitations cannot be read into the claims from the specification. Claim 59 does not recite that some cells are contacted with the "*exogenous bioactive agent precursor*" and some are not. The claim recites "*contacting said cells, prior to screening, with a library of exogenous bioactive agent precursors.*"

6C. Claim 65 remains rejected over the term "*targeting sequence*" for reasons made of record in Paper No. 28.

Applicants argue that page 16[17], lines 11-20 of the specification provides descriptions of targeting sequences. While page 17, lines 11-20 of the specification provides a non-limiting list of examples of targeting sequences, no definition which would allow one of ordinary skill in the art to determine the metes and bounds of the term is present.

6D. Claim 66 remains rejected over the term "*rescue sequence*" for reasons made of record in Paper No. 28.

Applicants argue that rescue sequences are "*fusion partners*" share a common functionality that "*allows purifying or isolating scaffolds, enzymes, or enzyme complexes, or nucleic acids encoding them.*" Applicants' argument has been carefully considered and found not to be persuasive. Any fusion partner has the potential to be a "rescue sequence" because, in principle, any peptide sequence can be bound by an antibody or other ligand and any nucleic acid sequence can be hybridized to its complementary sequence. One of ordinary skill in the art would not know what distinguishes a "*rescue sequence*" from any other sequence.

6E. Claim 67 remains rejected over the term "*stability sequence*" for reasons made of record in Paper No. 28.

Applicants argue that page 22, lines 23-24, of the specification describes a stability sequence as a sequence conferring stability to the "*expression products or the nucleic acids encoding them.*" Applicants state that poly A tails, cap structures, and 5' and 3' non-translated sequences are to be included. One of ordinary skill in the art would not be able to determine the metes and bounds of the claimed invention because one would not know what sequences are NOT encompassed by the term. According to applicants' description, any part of any molecule could reasonably be considered a "stability sequence."

Maintained Rejections – 35 U.S.C. 102

A supplemental reference is provided to applicants solely for the purpose of answering applicants arguments concerning the inherent quaternary structure of the enzyme complexes cited in the rejections under 35 U.S.C. 102 and 103. The reference is Pikus et al. Biochemistry (1996) 35(28):9106-9119 and it provides more detailed information than the references cited in the following rejections about the precise structures of pseudomonas oxygenase and dioxygensase complexes. The Pikus et al. reference discloses the quaternary structure of a multisubunit enzyme representative of bacterial oxygenases (see abstract, and page 9117, column 1).

7. Claims 58, 59-62, 64-66, 68, 69, 72, 77, and 78 remain rejected under 35 U.S.C. 102(e) as being anticipated by Khosla et al. U.S. Patent No. 5,672,491, September, 1997 (filed May 6, 1994) for reasons made of record in Paper No 28.

Applicants argue that Khosla et al. do not indicate how the subunits of PKS are arranged in the assembly and that the multifunctionality of PKS "*relates to the presence of numerous catalytic activities (e.g. clusters or modules) within a single polypeptide of PKS rather than a description of physical arrangements of the PKS enzymes.*" Applicants' arguments have been carefully considered and found not to be persuasive. Column 1, lines 61-64, of Khosla et al. reads as follows:

"*These 'complex' or '**modular**' PKSs include **assemblies** of **several** large multifunctional **proteins** carrying, between them, a set of separate active sites for each step of carbon chain assembly and modification.*" (emphasis added)

Column 15, lines 1-7, of Khosla et al. discloses an example of a modular PKS made of three polypeptides. Three interacting polypeptides inherently read on two enzymes and a scaffold because a scaffold is any nucleic acid or polypeptide that can bind two enzymes. In a trimeric structure, at least one of the subunits must be in contact (i.e. bound to) the other two subunits and therefor reads on a scaffold. "*Modular*" PKSs are disclosed in column 1, lines 59-66, as including assemblies of several multifunctional proteins. One of ordinary skill in the art would have understood the term "*modular assembly of several proteins*" to mean a multimeric protein of more than one subunit. Consequently, such proteins (enzymes) are inherently included within the scope of the Khosla et al. method.

8. Claims 58, 59, 63-70, and 74-79 remain rejected under 35 U.S.C. 102(e) as being anticipated by Minshull et al. U.S. Patent No. 5,837,458 November 1998(filed May, 1996) with Srere (1987) Annual Review of Biochemistry 56:89-91 cited in support of the inherency of "*scaffolds.*"

Applicants argue that Minshull et al. do not expressly teach the expression of enzymes that physically interact, only enzymes acting in metabolic pathways and that the Srere reference is insufficient to differentiate or identify enzymes vs. enzymes that act as scaffolds.

Applicants' arguments have been carefully considered and found not to be persuasive. Column 7, lines 15-27, of Minshull et al. discloses that the method "*is also useful for exploring permutations of any other multi-subunit enzymes. An example of such enzymes composed of*

multiple polypeptides that have shown novel functions when the subunits are combined in novel ways are dioxygenases. Directed recombination between the four protein subunits of biphenyl and toluene dioxygenases produced functional dioxygenases with increased activity against tricholorethylene (reference). This combination of subunits from the two dioxygenases could also have been produced by cassette-shuffling of the dioxygenases as described above, followed by selection for degradation of trichloroethylene." Column 20, lines 17-21 and lines 41-49, discloses the use of that method to evolve dioxygenases and two multi-component oxygensases.

Consequently, the Minshull et al. reference clearly discloses the use of their "*evolving*" method with multisubunit enzymes, which inherently involve "*scaffolds*" as defined in the present specification. At least one subunit of the enzyme must inherently bind to at least two other subunits to form a tetramer, for example.

With respect to the Srere reference, a complete copy of the article is provided with this office action. As the entire volume is over 1000 pages in length and the other articles are not directed to the same topic and are written by other authors, the entire volume is not provided.

Maintained Rejection – 35 U.S.C. 103

9. Claims 71 and 73 and newly added claim 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minshull et al. U.S. Patent No. 5,837,458.

Applicants argue that the cited reference fails to teach or suggest the expression of scaffolds and their introduction into cells via retroviral vectors.

Applicants' arguments have been carefully considered and found not to be persuasive. Applicants argument with respect to scaffolds was addressed in the answers to applicants' arguments traversing the rejections under 35 U.S.C. 102. With respect to retroviral vectors, the Minshull et al. teaches that virus-virus recombination involving viruses that are not lethal to the host cell and virus-chromosome recombination can be used in their method (column 10 lines 55-65 and column 12, lines1-22). It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use a retroviral vector in the method of Minshull et al. The examiner maintains that one would have been motivated to use retroviral vectors because are one of a small number of classes of viruses, they were commonly used to transform cells, not

lethal, and would be particularly well suited for work in cell lines that known to be infected by retroviruses (e.g. B cells). One would have had a reasonable expectation of success because the use of retroviral vectors was routine in the art at the time that the invention was made.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Tomas Friend, Ph.D.
08 June 2002

DR. JYOTHSNA VENKAT PH.D
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